1. Hypothesis and Objectives

The hypothesis of the proposed clinical trial is that anti-tumor activity of vaccinia-PSA (the study drug, a recombinant vaccine designed to activate T cells which specifically eliminate PSA-expressing prostate cancer cells) can be induced most effectively by:

a) Reducing immunological anergy and tolerance signals associated with expression of PSA in normal prostate cells

b) Minimizing tumor burden via surgery and androgen deprivation

c) Restricting vaccination to patients in whom all PSA expressing cells are cancerous (i.e. patients without normal prostate tissue; those who have previously undergone radical prostatectomy)

This hypothesis will be evaluated by a clinical Phase I/II study addressing three objectives. The objective of the Phase I dose escalation will be to determine the maximum tolerated dose (MTD) of vaccinia-PSA administered via intradermal injection. The two objectives of the Phase II analysis will be to evaluate the immunological and serological (PSA response) anti-tumor effects of vaccinia-PSA. Although other clinical trials using vaccinia-PSA have been proposed, the focus on evaluating efficacy by measuring rate of change of serum PSA and the focus on use of androgen ablation following radical prostatectomy to reduce immune tolerance and anergy to PSA in this study are unique.

2. Background

2.1 Recombinant vaccine therapy of prostate cancer

Following the development of genetically modified tumor cell vaccines in non-prostate cancer models (Fearon, Gansbacher, Dranoff), we and others have previously evaluated the suitability of prostate cancer as a target for recombinant tumor vaccines. Initial studies evaluated the feasibility and efficacy of prostate cancer cells genetically modified to produce immuno-stimulatory gene products such as IL-2 and GM-CSF (Vieweg, Moody, Sanda). We found that intradermally administered prostate cancer cells transduced to secrete GM-CSF conveyed a significant rate of cure and overall survival advantage to treated rats compared to controls who received untransduced prostate cancer cell vaccine (Figure 1). Significant therapeutic benefit was also demonstrated by other investigators in studies using prostate cancer cell vaccines transduced with IL-2 or murine GM-CSF (Vieweg, Moody). These investigators demonstrated the role of the T-cell mediated immune response in the therapeutic in vivo effect in the Dunning rat model. Clinical trials based on these studies and using patient-derived prostate cancer cells as a source of genetically modified autologous prostate cancer vaccines have recently been undertaken (Simons). However, prostate cancer cells for culture and transduction are not readily accessible in all patients (e.g. patients with recurrence following radical prostatectomy). The requirement for harvest and culture of autologous cancer cells and other limitations of gene-modified cancer cell vaccines have led to the evaluation of direct viral vaccines encoding tumor-associated antigens as an alternative therapeutic strategy.

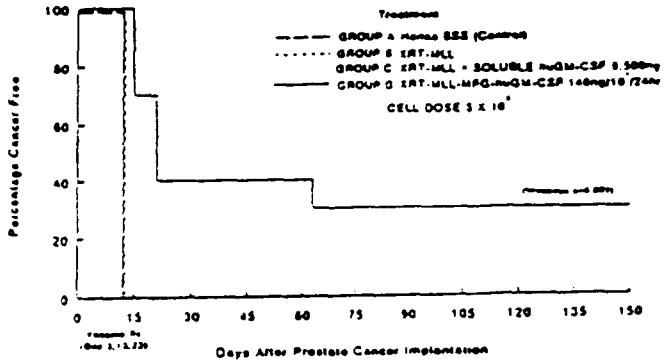


Figure 1. Preclinical Efficacy of a Genetically Modified Tumor Cell Vaccine for Therapy of Prostate Cancer. After being transduced to secrete high levels of GM-CSF, MatLyLu rat prostate cancer cells were used to treat pre-established microscopic prostate cancer. Tumor progression was delayed in 70% of treated animals, and 30% showed long-term cure. Control vaccine cells which were not genetically modified and systemic administration of GM-CSF were ineffective (Sanda et al. J Urol 151:622-8, 1994)

2.2. Poxvirus vaccines encoding tumor associated antigens and their utility in a preclinical model of prostate cancer.

Other investigators had previously demonstrated the utility of poxvirus vaccines encoding model antigens in treating animal models of a variety of non-prostate tumors and clinical evaluation of such a strategy has been undertaken using vaccinia encoding CEA for the therapy of colon cancer (Kantor, Bronte). These studies and the development of recombinant vaccinia encoding PSA (Hodge) prompted us to evaluate the susceptibility of prostate cancer to vaccinia immunization in the Dunning rat prostate cancer model. Because neither normal rat prostate nor Dunning prostate cancer cells express a homologue of PSA, we used b-galactosidase as a surrogate tumor-associated antigen (TAA) for these studies. Immunization of rats with vaccinia encoding this surrogate antigen reduced and in some cases prevented prostate cancer progression after subsequent implantation of Dunning prostate cancer cells expressing b-galactosidase (Figure 2).

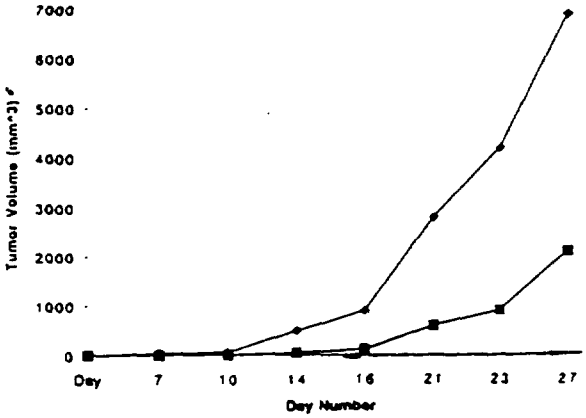


Figure 2. Preclinical Efficacy Against Prostate Cancer of a Recombinant Vaccinia Vaccine. Reduction in prostate cancer progression ($p<0.01$, left) and prolongation of tumor-free survival ($p<0.01$; not shown) were seen in rats immunized with recombinant vaccinia virus encoding b-galactosidase as a model TAA (squares) compared to controls (circles) vaccinated with vaccinia lacking b-galactosidase, showing TAA specificity of the therapeutic effect (from Sanda et al., manuscript in preparation).

2.3 Vaccinia-PSA: targeting prostate cancer cells via their expression of PSA as an antigenic target of vaccine-induced T cells

Based on a variety of preclinical studies and toxicology analyses, the NCI has made available a recombinant vaccinia encoding human PSA (rV-PSA) as a substrate for human clinical trials (Hodge). This agent is a rational clinical extension of preclinical vaccinia studies showing the efficacy of recombinant vaccinia vaccines in treating or preventing cancers based on induction of an immune response against tumor-associated antigens expressed by specific cancer cells. The goal of immunization with vaccinia-PSA is to target cells which express PSA for recognition and lysis by activated T cells after effective vaccination.